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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,413	01/09/2006	Guy Sauvageau	765/12810.191	5322

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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
04/13/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/530,413	SAUVAGEAU ET AL.	
	Examiner	Art Unit	
	Catherine S. Hibbert	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,11-15,17-24,26-39 and 41-44* is/are pending in the application.

4a) Of the above claim(s) *1,9,11-15,17-24,26-30 and 41-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-38 and 44* is/are rejected.

7)☒ Claim(s) *39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/17/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is the First Action on the Merits of US Application 10/530,413, which is a National Stage Entry of PCT Application PCT/CA2003/001539, filed on 6 October 2003, which claims priority to U.S. Provisional Application 60/416,545, filed on October 8, 2002. Claims 1, 9, 11-15, 17-24, 26-39 and 41-44 are pending. Claims 2-8, 10, 16, 25 and 40 are cancelled. Claims 1, 9, 11-15, 17-24, 26-30 and 41-43 are withdrawn. Claims 31-39 and 44 are under examination in this action.

Election/Restrictions

Applicant's election with traverse of Group IV (Claims 31-39 and 44) and of the species:

1) "human" as the type of hematopoietic cells;

2) "an effective amount of a factor as defined in claim 1"; and

3) "in vitro" as the type of treatment between in vitro, in vivo and ex vivo,

in the reply filed on 21 November 2008 is acknowledged. The traversal is on the ground(s) that Applicant states that Applicant complies with the requirement of unity of invention for the following reason. Applicants submit that Groups I-VII, and all listed species are linked by at least one single general inventive concept that is not anticipated or made obvious over the Buske reference because Applicants state that Buske does not disclose or suggest that PBX1 inhibits HOXB4-induced expansion.

This is not found persuasive for the reasons provided in the Office Action mailed 11 January 2008 which shows that the special technical feature that links the inventive groups is a blocker which reduces expression level of at least one gene normally

limiting HOX-induced expansion of stem cells, whereby reducing expression level of said gene enhances expansion of stem cells containing a HOX peptide. Accordingly, Buske et al in "Deregulated expression of HOXB4 enhances the primitive growth activity of human hematopoietic cells" (Blood, 1 August 2002, Vol.,100, No:3, pp. 862-868, made of record in the Restriction Requirement mailed 11 January 2008), anticipates the special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 9, 11-15, 17-24, 26-30, and 41-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 21 November 2008.

Information Disclosure Statement

The information disclosure statement filed 17 August 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Specifically, the lined-through reference (citation 5, Bhardwaj et al) is missing and the information referred to therein has not been considered.

Claim Objections

Claim 39 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Claims 31-38 and 44 are objected to because of the following informalities: The claims all depend from a withdrawn claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 (and therefore dependent claims 32-38) are indefinite because it is unclear whether the phrase “for a time sufficient to allow expansion of said stem cells” refers only to “an effective amount of a composition as defined in claim 15” or whether it also is meant to limit the phrase “an effective amount of a factor as defined in claim 1”.

Additionally, Claim 32 recites the limitation "said HOX peptide" in line 1. There is insufficient antecedent basis for this limitation in the claim because the antecedent basis is found in the withdrawn Claim 1.

Additionally, Claim 33 is indefinite because the phrase "further comprising a step of treating said stem cell a HOX peptide encoded by a HOX nucleotide sequence" appears to be missing a word between "cell" and "a".

Additionally, Claims 34-35 (and therefore dependent Claim 36) recite the limitation "said amino acid sequence" in line 1. There is insufficient antecedent basis for this limitation in the claims because amended Claim 33, from which Claims 34 and 35 depend, has deleted out the reference to “an amino acid sequence” and presently does not refer to an amino acid sequence.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-38 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass the provision of a genus of stem cell expansion factors. The stem cell expansion factors are defined by the claims as comprising an amino acid sequence having the expansion enhancement activity of a peptide encoded by a Hox nucleotide sequence enhancing expansion of a stem cell population, and wherein the factor is able to cross a cell membrane. The rejected claims thus comprise a genus of

proteins that are defined by function: (1) have the enhancement activity of a hox peptide, and (2) are capable of crossing the cell membrane.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. As shown in the instant specification, the hox proteins do not share the common property of enhancing all stem cell expansion. The effect of the hox protein on the expansion of a particular stem cell type is dependent upon the structures that diverge between the different hox proteins.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of a few full-length hox proteins that are capable of expanding a stem cell population. The prior art teaches that mammals have 38 hox genes that are found in four clusters (Largman et al, US Patent No. 5,837,507; e.g., column 2, lines 28-30). Largman et al suggest that some of the hox genes may play a role in leukemogenesis (e.g., column 7, lines 29-34). The proteins that induce leukemia rather than cell expansion would not be suitable for use in the presently claimed invention. The results are not necessarily predictive of which hox proteins will have the desired function. Even if a representative number of hox proteins have the desired effect, the specification and prior art do not provide guidance as to which domains within the hox proteins are sufficient to provide the claimed function, and the claims read on

the administration of less than the full-length protein and sequences that have the same function but are not necessarily obtained from a hox protein. Thus, it is impossible for one to extrapolate from the few examples described herein those proteins that would necessarily meet the structural/functional characteristics of the rejected claims. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

Given the very large genus of proteins encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to specific domains or sequences required for stem cell expansion activity, the skilled artisan Would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly

claimed genus of proteins. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those proteins that satisfy the functional limitations of the claims with regard to stem cell expansion activity. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 31-38 and 44.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 31-38 and 44 are rejected under 35 U.S.C. 102(a) as being anticipated by Buske et al in "Deregulated expression of HOXB4 enhances the primitive growth activity of human hematopoietic cells" (Blood, 1 August 2002, Vol.,100, No:3, pp. 862-868, made of record in the Restriction Requirement mailed 11 January 2008).

Claims 31/32 read on a method comprising: treating stem cells with an effective amount of "a factor comprising a blocker which reduces expression level of at least one gene normally limiting HOX-induced expansion of stem cells, whereby reducing expression level of said gene enhances expansion of stem cells containing a HOX/HOXB4 peptide". Claims 37/38 specify within Claim 31 that said stem cells are hematopoietic stem cells/human hematopoietic stem cells.

Claim 33 is drawn to the method of Claim 31, further comprising a step of treating said stem cell "with" a HOX peptide encoded by a HOX nucleotide sequence. Claim 34

specifies within Claim 33 that said amino acid sequence consists of a HOXB4 peptide. Claim 35 specifies within Claim 33 that said amino acid sequence comprises an HIV-derived peptide able to cross a cell membrane. Claim 36 specifies within Claim 35 that said HIV-derived peptide consists of a NH2-terminal protein transduction domain (PTD) from a transactivating protein.

Claim 44 is directed to a method for enhancing expansion of stem cells, which comprises treating stem cells with an effective amount of a factor comprising "a blocker which reduces expression level of at least one gene normally limiting HOX-induced expansion of stem cells, whereby reducing expression level of said gene enhances expansion of stem cells containing a HOX peptide" for a time sufficient to allow expansion of said stem cells.

Buske et al teach treating said stem cell with a HOX peptide encoded by a HOX nucleotide sequence. Buske et al teach a blocker which reduces expression level of at least one gene normally limiting HOX-induced expansion of stem cells, whereby reducing expression level of said gene enhances expansion of stem cells containing a HOX peptide (e.g. abstract and Figure 1 and legend). Buske et al teach a method for enhancing expansion of stem cells, which comprises treating stem cells with an effective amount of a factor comprising "a blocker which reduces expression level of at least one gene normally limiting HOX-induced expansion of stem cells, whereby reducing expression level of said gene enhances expansion of stem cells containing a HOX peptide" for a time sufficient to allow expansion of said stem cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 35 and 36 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Largman et al (US Patent No. 5,837,507, see the entire reference) in view of Frankel et al (US Patent No. 5,804,604; see the entire reference).

Largman et al teach the expression of an exogenous HOX gene, preferably HOXB4, in a stem cell to generate expanded populations of pluripotent stem cells *in vitro or in vivo* (e.g., Abstract; column 2, lines 35-59; column 8, lines 5-38; column 11, line 53 to column 12, line 50). The preferred stem cell is a hematopoietic stem cell, such as a human hematopoietic stem cell expressing the cell surface marker CD34 (e.g., column 2, lines 48-59). Largman et al teach that it is the expression of the HOXB4 gene (i.e., the HOXB4 protein) that results in the desired function (e.g., column 12, lines 5-37).

Largman et al do not teach the method where the HOXB4 protein is delivered to the stem cell by crossing the cell membrane as a result of the presence of a HIV-TAT protein.

Frankel et al teach the delivery of biologically active proteins to the cytoplasm and nuclei of cells *in vitro and in vivo* by the use of transport polypeptides which comprise HIV tat protein, which are covalently attached to the cargo protein (e.g., Abstract; column 1, lines 20-40; column 2, line 64 to column 4, line 3; column 7, lines 23-38). Frankel specifically teach the delivery of a transcription factor by TAT mediated protein transduction (e.g., column 12, lines 25-40). Further, Frankel et al teach that methods of DNA delivery typically deliver the nucleic acid molecules into only a fraction of the total cell population and tend to damage large numbers of cells (e.g., column 1, lines 54-63). In contrast, the methods of using the tat protein to deliver proteins provide efficient delivery of non-tat proteins that are not inherently capable of entering target

cells or nuclei, or are not inherently capable of entering cells at a useful rate (e.g., column 3, lines 6-15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of generating expanded populations of stem cells of Largman et al to replace the delivery of HOXB4 protein by delivering a nucleic acid molecule with the delivery of HOXB4 protein by delivering a tat-conjugated protein as taught by Frankel et al because Largman et al teach it is within the ordinary skill in the art to use HOXB4 protein expression to expand populations of stem cells and Frankel et al teach the delivery of proteins to cells *in vitro* and *in vivo*.

One would have been motivated to make such a modification in order to receive the expected benefit of more efficiently delivering the HOXB4 protein to the nucleus of the cells as taught by Frankel et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31-38 and 44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7, 9,12 and 13 of copending Application No. 10/727,580 (herein '580 application).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. *In re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman,* 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because amended claims 31-38 and 44 are now generic to or essentially identical to all that is recited in the presently amended copending claims 7, 9,12 and 13 of the '580 application. In other words, instant claims 31-38 and 44 are anticipated by claims 7, 9,12 and 13 of the '580 application. The claims of the '580 application are narrower in scope than the instant claims in that they require the limitations of the instant dependent claims in the copending base claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine S. Hibbert whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully submitted,

Catherine S. Hibbert
Examiner/AU1636

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1636